stabilizer a member selected from the group consisting of proteins, buffers, saccharides and mixtures thereof.

27. The method of claim 20, wherein said osteoclastgenic inhibitory composition is in the form of a member selected from the group consisting of liquids, pastes, and solids.

REMARKS

The Office Action and the cited and applied references have been carefully studied. No claims are allowed. Claims 1-6, and 8-27 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The specification has been objected to in the numbering of the examples, which should be consecutive. The examiner indicates that Examples 1-9 are listed, but then Examples 1-4 are listed starting at page 36. This objection is respectfully traversed.

Example 1 to Example 8 on pages 36-39 are distinguished from Experiment 1 (not Example 1) to Experiment 8 on pages 11-36. The numbered experiments relate to exemplified experiments whereas the numbered examples relate to different formulations/preparations of the osteoclastgenic inhibitory composition of the present invention. Accordingly, these is no need to renumber, as the Experiments are

distinguished from the Examples and one of skill in the art reading the specification would recognize the difference.

The examiner finds the title of the invention to be not descriptive. A new titled is required. The title helpfully suggested by the examiner is adopted.

Claims 1-11 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendments to the claims.

With regard to claims 2-4 and 6, it is clarified that the effective ingredient comprises each of the recited amino acid sequences, and presently amended claims 2 and 6 are indeed definite in this regard. Whether or not these sequences are contiguous or in tandem is irrelevant. All that is needed to make the claims definite is that the effective ingredient comprises the recited sequences within its full length amino acid sequence.

Claim 11 has been rejected under 35 U.S.C. §112, first paragraph, because the examiner finds that the specification, while being enabling for treating some osteoclast-related diseases, does not reasonably provide enablement for the aspect of "preventing", nor is there enablement for treating or preventing the full scope of "osteoclast-related diseases". This rejection is respectfully traversed.

While applicants do not concede that the aspect of "preventing" is not enabled, this part of the rejection is

made moot by the deletion of the recitation of "preventing" in claim 11 to further prosecution. Claim 11 is also amended to recite "treating a disease associated with excessive osteoclast formation or activity" as supported by the specification at page 9, where a representative number of such diseases is exemplified. Based on disclosure of the many diseases associated with excessive osteoclast formation or activity, one of skill in the art can certainly determine the scope of such diseases associated with excessive osteoclast formation or activity.

Furthermore, it is respectfully pointed out that, at the time the invention was made, it was known that GM-CSF could be used in treating and/or preventing diseases associated with excessive osteoclast formation or activity. The present specification discloses that (1) IL-18 induces the production of GM-CSF (Experiment 7-1, pages 14-26), (2) IL-18 has an activity of inhibiting osteoclast-like cells (OCL) formation *in vitro* and also inhibits osteoclast formation (experiment 7-2 (a)) due to the action of GM-CSF inducing activity of IL-18 (Experiment 7-2(c)). Therefore, it would be quite credible to those of skill in the art (certainly more credible than not), based on the experiments presented in the specification that the osteoclast inhibitory activity is due to the action of GM-CSF induced by IL-18, to consider IL-18 as an effective osteoclastgenic inhibitor for treating a disease associated with excessive osteoclast formation or activity.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1 and 7-11 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for IL-18 having the full length or certain partial sequences and to methods of treatment using such, does not reasonably provide enablement for:a) any osteoclastgenic innibitor of unspecific characterization that is merely referred by the name, as in claim 1, or for peptides from any specie form of the IL-18, (b) any "functional equivalent", and (c) the treatment or prevention of the broad array of osteoclast-related diseases with the various small peptides of the claims. This rejection is respectfully traversed.

Independent claims 1, 12, and 20 are now amended to recite "interleukin-18 comprising the amino acid sequence of SEQ ID NO:6 or a functional equivalent thereof". SEQ ID NO:6 is the amino acid sequence of human IL-18 and thus a structure of human IL-18 is characterized/defined in the claims. With regard to functional equivalents of the human IL-18 of SEQ ID NO:6, the specification provides guidance on the functional equivalents to be encompassed in the scope of the claims. Three specific functional equivalents are exemplified in Experiments 3 (pages 14-16), 4 (pages 16-18) and 6 (pages 19 and 24) and functional equivalents are discussed on pages 4-6 of the specification, with a teaching of the preferred amino

acids for replacing cysteine residues. As SEQ ID NO:7, the amino acid sequence of mouse IL-18, is provided in the specification and specifically exemplified in Experiment 6 (pages 19-24), one of skill in the art can readily align the amino acid sequences of human IL-18 (SEQ ID NO:6) and mouse IL-18 (SEQ ID NO:7), an alignment from which the consensus sequences of SEQ ID NOs:1, 2, and 4 were identified as discussed on page 8 of the specification. From this alignment, one of skill in the art can identify the sequence homology between human IL-18 and mouse IL-18 and where sequences are conserved and where sequence conservation does not appear to be critical. Accordingly, based on the guidance provided by the teachings of functional equivalents in the specification and the amino acid alignment of two homologous IL-18s, one of skill in the art is quite enabled for the scope of functional equivalents as presently claimed.

On the matter of what the examiner considers to be peptides from any specie of IL-18, applicants clarify that the claims are directed to human IL-18 comprising SEQ ID NO:6 or functional equivalents thereof. Claims 2, 3, 13, 14, 21, and 22 recite that the IL-18 or a functional equivalent thereof comprises partial amino acid sequences and is not intended to comprehend small peptides containing the short amino acid sequences of SEQ ID NOs: 1-6.

With regard to point (c), the enablement for "preventing" osteoclast-related diseases is made moot by the

cancellation without prejudice of the recitation of "preventing" from the claims. The enablement for treating diseases associated with excessive osteoclast formation or activity is discussed above in the previous enablement rejection of claim 11.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1-10 have been rejected under 35 U.S.C. §101 because the claimed invention is indicated as being directed to non-statutory subject matter. This rejection is obviated by the amendment to claims 1-10.

Claims 1, 7-10, and claims 2-6 have been rejected under 35 U.S.C. §102(?) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Ushio et al., Okamura et al. ('324) or Sana ('468). The examiner states that each of the applied prior art references discloses a protein that is now known as IL-18 and that has the same sequence as that recited in the claims or is considered inherent. This rejection is respectfully traversed.

Claim 1 is presently directed to an osteoclastgenic inhibitory composition that comprises human IL-18 or a functional equivalent thereof as an effective ingredient and a pharmaceutically-acceptable carrier. Ushio (The Journal of Immunology 156:4274-4279, 1996) and Okamura (U.S. Patent 5,912,324) do not disclose a pharmaceutical composition

comprising an osteoclastgenic inhibitor (IL-18) and a pharmaceutically-acceptable carrier. Sana et al. (WO 97/44448) only discloses IL-1γ which consists of 194 amino acid residues. Sana discloses nothing about a human IL-18 having 157 amino acid residues. Applicants believe that Sana teaches nothing about the presently claimed invention. Accordingly, neither Ushio, Okamura, nor Sana can anticipate or make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1 and 7-11 have been rejected under 35 U.S.C. §102(b) as being anticipated by or in the alternative, under 35 U.S.C. §103(a) as being obvious over Udagawa et al. (J. Exp. Med. 1998). The examiner indicates that these claims are being rejected based on the limitation of the claims for "functional equivalent", where the examiner asserts that the prior art teaches that IL-6 possesses osteoclastgenic inhibitory activity, and therefore reasonably appears to meet the limitations of the claims because the claims do not state that the functional equivalent has to be a portion of the IL-18 protein. This rejection is respectfully traversed.

Contrary to the examiner's assertion, Udagawa discloses that IL-6 stimulates osteoclast formation (see Summary on page 1461). Accordingly, Udagawa cannot anticipate or make obvious the present claims where IL-18 or a functional

derivative thereof inhibits (not stimulates) osteoclast formation.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 1 and 7-11 have been rejected under 35 U.S.C. §102(a) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Udagawa et al. (J. Exp. Med. 1997) or Martin et al. (1998). The examiner states that each of the art teaches that IL-19 has osteoclastgenic activity, and therefore meets the limitation of the claims. The examiner also indicates that with regard to this particular rejection, it is pointed out that the authorship and inventorship differs, and applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. This rejection is respectfully traversed.

In a telephone conference with the examiner on October 31, 2000, for which an Examiner's Interview Summary is made of record in the file, the examiner indicated that the translation of the foreign priority document is indeed in the application file. As the publication date of the applied Udagawa reference is March 17, 1997, and the publication date of the applied Martin reference is in 1998, both are not available as prior art references against the present claims,

which are entitled to the benefit of the February 25, 1997, filing date of the Japanese priority document.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

1. An osteoclastgenic inhibitory composition ~~agent~~, which comprises a pharmaceutically-acceptable carrier and an interleukin-18 comprising the amino acid sequence of SEQ ID NO:6 or ~~its~~ a functional equivalent thereof as an effective ingredient, said interleukin-18 or a functional equivalent thereof being capable of exerting osteoclastgenic inhibitory activity.

2. The inhibitory composition ~~agent~~ of claim 1, wherein said interleukin-18 or a functional equivalent thereof ~~includes~~ comprises each of the amino acid sequences of SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3 ~~as partial amino acid sequences~~.

3. The inhibitory composition ~~agent~~ of claim 1, wherein said interleukin-18 or its functional equivalent thereof ~~includes~~ comprises both the amino acid sequences of SEQ ID NO:4 and SEQ ID NO:5 ~~as partial amino acid sequences~~.

4. The inhibitory composition ~~agent~~ of claim 1, wherein said effective ingredient is interleukin-18 ~~includes~~ comprising the amino acid sequence of SEQ ID NO:6.

5. The inhibitory composition ~~agent~~ of claim 1, wherein said interleukin-18 is of human origin.

6. The inhibitory composition ~~agent~~ of claim 1, wherein said functional equivalent of interleukin-18 ~~includes~~ comprises the amino acid sequence of SEQ ID NO:7.

8. The inhibitory composition ~~agent~~ of claim 1, which ~~contains~~ further comprises as a stabilizer a member selected from the group consisting of ~~a~~ proteins, buffers, ~~or~~ saccharides, and mixtures thereof ~~as a stabilizer~~.

9. The inhibitory composition ~~agent~~ of claim 1, which is in the form of a member selected from the group consisting of ~~a~~ liquids, pastes, ~~or~~ and solids.

10. The inhibitory composition ~~agent~~ of claim 1, which contains 0.000002-100 w/w% of said interleukin-18.

11. A method for treating ~~and/or preventing osteoclast-related diseases~~ a disease associated with excessive osteoclast formation or activity, ~~which~~ comprising administering said inhibitory composition ~~agent~~ of claim 1 to patients suffering from said ~~diseases~~ disease at a dose of about 0.5 μg to 100 mg per shot, 2 to 6 fold a day or 2 to 10 fold a week ~~for~~ from one day to one year.